World J. Surg. 20, 5–10, 1996

WORLD
Journal of
SURGERY

Original Scientific Reports

Hypercoagulability following Multiple Trauma

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Abstract. We sought evidence of hypercoagulability in 59 seriously injured trauma patients. An extended coagulation profile (consisting of tissue plasminogen activator antigen concentration, plasminogen activator inhibitor, serum antithrombin III, protein C antigen, functional protein C, protein S antigen, D-dimer, and prothrombin fragment 1.2) was compared to control values. Laboratory evidence of hypercoagulability was seen in 85% ($n = 50$) of the patients. Patients with an Injury Severity Score (ISS) ≥ 16 ($n = 36$) had significantly elevated levels of D-dimer and decreased levels of functional protein C compared to patients with an ISS ≤ 15 ($n = 23$). Functional protein C had a negative correlation ($r = -0.44$; $p < 0.001$) with the ISS. A hypercoagulable state exists immediately following severe trauma. Greater injury severity may increase this hypercoagulable state. Decreased levels of functional protein C best correlated with increased injury severity.

In a dog bled to death by the removal of blood from a vein in successive portions, the last portions often coagulate almost instantaneously.

Cohnheim, 1877 [1]

During the nineteenth century Virchow defined three factors that promoted deep venous thrombosis (DVT): stasis, abnormalities of the vessel wall, and alterations in the blood coagulation system [2]. Trauma patients are at particularly high risk for the development of DVT [3]. Prolonged immobilization, lower extremity and pelvic fractures, and acute neurosurgical injuries have all been associated with an increased risk of DVT [3]. The Consensus Conference of the National Institutes of Health estimated that the incidence of DVT in the young patient with multisystem trauma is approximately 20% [4].

A subgroup at an even greater risk of developing DVT are patients with a degree of injury significant enough to warrant admission to a trauma resuscitation room. Patients triaged to acute resuscitation rooms have a high incidence of injuries that would be expected to require long periods of bed rest with an increased risk for venous stasis [2]. Just as importantly, these patients may be in a hypercoagulable state secondary to extensive tissue trauma.

The multiply injured trauma patient suffers from a compendium of disorders, each of which may alter the endogenous coagulation profile. A posttraumatic hypercoagulable state may result in which small, but significant, abnormalities occur among different coagulation parameters in different patients. In this prospective study we attempted to identify early alterations in the endogenous coagulation and fibrinolytic systems that may contribute to hypercoagulability in the multiple trauma patient. We also looked for a relation between injury severity and laboratory evidence of a hypercoagulable state.

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Materials and Methods

All adult patients entering Hartford Hospital from December 2, 1991 through July 6, 1992 with multiple trauma significant enough to warrant admission to the trauma resuscitation room were candidates for inclusion into the study. Excluded were any pediatric trauma patient (age < 16 years), patients with isolated head injuries, patients with documented DVT or pulmonary embolus, or any unresuscitatable patients. The study was approved by the Hartford Hospital Institutional Review Committee. Informed consent was obtained from all patients or their families.

Fifty-nine severely injured trauma patients (40 men, 19 women) were entered into the study. Each of the patients had blood samples withdrawn along with their initial blood work in the trauma resuscitation room, usually via femoral puncture. The eight parameters that were studied in the blood samples included tissue plasminogen activator antigen concentration (tPA), plasminogen activator inhibitor (PAI-1), serum antithrombin III (SAT), protein C antigen (PrC), functional protein C (FPrC), protein S antigen (PrS), D-dimer, and prothrombin fragment 1.2 (PF1.2). The changes that would be expected in each of these parameters in a state of hypercoagulability are summarized in Table 1 [5–10].

A total of 19 ml of blood was required for each set of tests. The blood work was performed in the following order. A 6-ml aliquot was placed in a clot activator tube to determine the SAT levels, 3 ml in a tube containing 72 USP of lithium heparin to determine PF1.2 levels, and 5 ml in each of two test tubes containing 3.8% buffered citrate solution to determine tPA, PAI-1, FPrC, PrC,

Table 1. Factor levels associated with hypercoagulability.

Factor	Hypercoagulable changes
Tissue plasminogen activator (tPA)	Decreased
Plasminogen activator inhibitor (PAI-1)	Increased
Serum antithrombin III (SAT)	Decreased
Protein C antigen (PrC)	Decreased
Functional protein C (FPrC)	Decreased
Protein S antigen (PrS)	Decreased
D-Dimer	Increased
Prothrombin fragment 1.2 (PF1.2)	Increased

Table 2. Patients within hypercoagulable range for each factor.

Factor	Control (normal) values (mean ± SEM)	Hypercoagulable values (no.)	No. of pts. with hypercoagulable values
tPA (ng/ml)	6.3 ± 0.5	< 1	0
PAI-1 (IU/ml)	5.7 ± 1.1	> 15	31 (53%)
SAT (%)	101.0 ± 5.0	< 65	15 (25%)
PrC (%)	102.0 ± 2.7	< 65	13 (22%)
FPrC (%)	112.0 ± 7.8	< 65	13 (22%)
PrS (%)	93.0 ± 3.6	< 65	9 (15%)
D-Dimer (μg/ml)	0.25 ± 0.03	> 1	36 (61%)
PF1.2 (nm)	1.6 ± 0.16	> 3	27 (46%)

PrS, and D-dimer levels. Each of the tubes was then gently inverted several times.

The SAT tube was allowed to clot for 30 to 120 minutes at room temperature. All of the blood samples were subsequently centrifuged for 15 minutes at 3000 rpm. The SAT serum was then removed and placed in a freezer at −70°C. The plasma from the other samples was similarly separated and frozen. The specimens were then grouped and mailed on Dry Ice to Colorado Coagulation Consultants (Denver, CO, USA), where they were analyzed.

The PAI-1 activity was measured by adding a fixed amount of t-PA to undiluted plasma. Part of the tPA is rapidly inactivated by PAI-1. The residual tPA, in the presence of a stimulator, then converts plasminogen to plasmin. The amount of plasmin formed is directly proportional to the residual tPA activity and inversely proportional to the PAI-1 activity in the sample.

The SAT was tested using the serine protease inhibitor test. This functional assay measures the capacity of serum to neutralize a known amount of thrombin. The decreased thrombin activity is measured by adding the serum–thrombin mixture to a controlled fibrinogen solution. The clotting time is proportional to the SAT activity.

The D-dimer level was determined by exposing test samples to latex particles covered with anti-human D-dimer monoclonal antibodies. The D-dimer levels can then be determined by the resulting agglutination reaction.

The levels of tPA, PrC, PrS, and PF1.2 were each measured using an enzyme-linked immunosorbent assay (ELISA). FPrC is a functional qualitative test of protein C activity. FPrC uses a chromogenic method to measure protein C levels quantitatively.

Data collection on each patient included the patient's age, gender, specific injuries, Injury Severity Score (ISS) [11], risk factors for thrombotic disorders, length of stay in the intensive care unit (ICU), and total hospital length of stay. Values were expressed as mean ± SEM. A Student's *t*-test was used to compare subgroups of patients with variable degrees of injury severity and control values. Spearman's correlation coefficient and the Bonferroni method were used to correlate injury severity with the laboratory results. Significance was accepted at a probability of less than 5% for the null hypothesis ($p < 0.05$).

Results

The 59 patients in the study group had a mean age of 37 years (range 16–89 years). Risk factors for thrombotic disorders included obesity in two patients and the use of birth control pills in one patient. None of the patients had a history of a thrombotic disorder.

Table 3. Comparison of factors among total patient group, patients with less severe and more severe injuries, and controls.

Factor	All patients ($n = 59$)	Less severe injury (ISS ≤ 15) ($n = 25$)	More severe injury (ISS ≥ 16) ($n = 34$)	Controls ($n = 19$)
tPA (ng/ml)	33.5 ± 9.7	17.2 ± 4.0*	45.4 ± 16.4	6.3 ± 0.5
PAI-1 (IU/ml)	17.4 ± 2.0*	16.8 ± 2.8*	17.9 ± 2.8*	5.7 ± 1.1
SAT (%)	77.4 ± 2.9*	80.7 ± 4.1*	75.0 ± 4.0*	101.0 ± 5.0
PrC (%)	83.3 ± 3.1*	89.8 ± 4.1*	78.5 ± 4.4*	102.0 ± 2.7
FPrC (%)	83.3 ± 3.6*	94.7 ± 4.2	74.9 ± 5.1*, **	112.0 ± 7.8
PrS (%)	90.1 ± 3.2	96.0 ± 3.8	85.7 ± 4.8	93.0 ± 3.6
D-dimer (μg/ml)	4.90 ± 0.91*	2.56 ± 1.27	6.62 ± 1.20*, **	0.25 ± 0.03
PF1.2 (nM)	3.85 ± 0.24*	3.20 ± 1.12	4.31 ± 0.49*	1.60 ± 0.16

Results are means ± SEM.
*$p < 0.05$ compared with controls; **$p < 0.05$ compared with ISS ≤ 15.

Ninety-seven percent of the patients sustained blunt trauma: 39 were in motor vehicle or motorcycle accidents, 10 were injured by a fall, 6 were pedestrians struck by motor vehicles, and 2 were victims of a crush injury. There were two patients with penetrating injuries. The mean ISS was 19 (range 1–50). All injuries occurred within 6 hours of hospital admission. There were three deaths (5.1% of the study group). The primary cause of death in all three cases was massive head injury with associated multiple trauma. For only one of the patients was an autopsy performed. The mean (± SEM) total hospital length of stay for the survivors was 24.3 ± 3.6 days, with a mean ICU length of stay of 9.3 ± 2.3 days.

Each of the coagulation tests was given a predetermined range of "abnormal hypercoagulability" based on controls (performed by Colorado Coagulation Consultants, who were responsible for analysis of the samples). Table 2 illustrates the normal values for each of the parameters tested, the hypercoagulable values, and the number and percent of patients whose values fell within this hypercoagulable range. Overall, 85% ($n = 50$) of the patients in the study had one or more hypercoagulable values.

The mean values for each of the tests for the overall group is seen in Table 3. Significantly decreased levels of PrC, SAT, and FPrC and increased levels of D-dimer, PF1.2, and PAI-1 were seen (compared to control values). Excessively elevated levels of tPA were seen in some patients, which resulted in large standard errors in this patient group, thereby limiting the statistical significance.

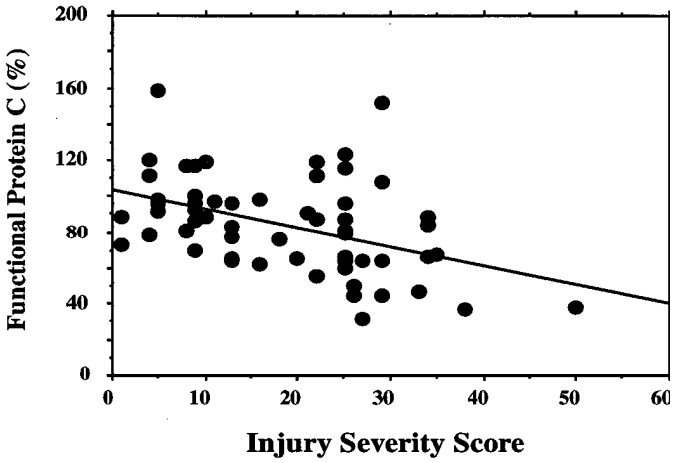

Fig. 1. Scatterplot showing relation of injury severity score to functional protein C value ($r = -0.44$; $p = 0.006$).

Each of the coagulation parameters was then plotted against the ISS using Spearman's correlation coefficient. The greatest correlation was found for FPrC, which had an r value of -0.44 ($p = 0.0006$) (Fig. 1). This p value was significant using the Bonferroni correction.

The patients were then divided into two groups based on injury severity: those with an ISS ≤ 15 and those with an ISS ≥ 16. An ISS ≥ 16 was chosen to represent the more severely injured group as these patients have a 10% or greater chance of dying from their injuries [12].

There were no significant differences in age or sex between the severely and the less severely injured patient groups. There was a significant difference in ICU days and total hospitalization time (Table 4). The mean values for each of the tests for the two groups are seen in Table 3. Significantly elevated levels of D-dimer and decreased levels of FPrC were seen in the more severely injured group compared to the values for the less severely injured group.

Discussion

Researchers have been interested in the effects of trauma on blood coagulation for more than 200 years. In 1772 Hewson noted that as an animal was exsanguinated its blood became hypercoagulable, a phenomenon that was confirmed by Nasse in 1842, Brücke in 1857, and Cohnheim in 1877. In 1914 Gray and Lunt theorized that the liver may be responsible for hastening coagulation following rapid exsanguination [1].

In 1964 Innes and Sevitt published a study looking at the serial changes in coagulation and fibrinolysis in 42 trauma patients. It was found that fibrinolysis was accelerated within the first few hours after injury, followed by a prolongation of fibrinolysis during the subsequent period. It was theorized that the acceleration was due to a plasminogen activator, and that the prolongation was due to an inhibitor. The location of the injury did not influence the extent of fibrinolysis. However, the injury severity affected the duration of accelerated lysis and possibly the subsequent prolongation [13].

Table 4. Comparison of less severely and more severely injured patient population groups.

Variable	Less severe injury (ISS $\leq$ 15) (n = 25)	More severe injury (ISS $\geq$ 16) (n = 34)
Age	34.3 ± 4.0	41.5 ± 3.6
Sex (% male)	60	74
ICU (days)	3.5 ± 1.1	13.5 ± 3.8*
Total hospitalization (days)	14.9 ± 3.1	31.9 ± 5.7*

Results are means ± SEM.
*$p < 0.05$ compared with ISS $\leq$ 15.

Tissue Plasminogen Activator and Plasminogen Activator Inhibitor

The enzyme plasmin is responsible for proteolytic degradation of fibrin clots (fibrinolysis), fibrinogen, blood clotting factors, membrane proteins, and proteins of the intercellular matrix. Circulating plasmin is formed from the inactive precursor plasminogen through the proteolytic action of plasminogen activators. The tissue-type plasminogen activator (t-PA) is responsible for conversion of plasminogen to plasmin. In the absence of fibrin, t-PA in circulating plasma does not cause any appreciable degree of plasmin formation and thus little fibrinolysis [14].

In 1963 a plasminogen activator inhibitor was first hypothesized in pregnant women [15]. By 1985 the endothelial cell-type plasminogen activator inhibitor was convincingly demonstrated and referred to as plasminogen activator inhibitor 1 (PAI-1) [16]. PAI-1 is a glycoprotein synthesized by endothelial cells and is present in plasma at a concentration two to three times that of t-PA. PAI-1 released from endothelial cells is stimulated by thrombin, dexamethasone, endotoxin, interleukin 1, transforming growth factor B, and tumor necrosis factor [17].

In plasma, most t-PA is bound to its inhibitor PAI-1, leaving less than 5% in the free, active form [14]. Circulating t-PA may be the most important component of hemostatic regulation following fibrin formation. Thus the levels of its inhibitor, PAI-1, are just as critical. Increased PAI-1 levels have been theorized to contribute to the increased incidence of thrombosis seen with infection [18], with coronary artery disease [19], and after surgery [20].

Various investigators have evaluated the levels of PAI-1 prospectively in high risk patients and attempted to correlate these levels with an increased incidence of DVT. Orthopedic, general, urologic, and gynecologic surgical patients who have developed postoperative DVTs have been shown to have low t-PA levels and high PAI-1 levels [21–24]. T-PA activity has been found to be suppressed in severely injured trauma patients. This suppression was not found to be correlated with trauma severity as measured by the ISS [5]. PAI-1 levels have been found to be elevated following two or more major fractures in one small study [6].

Our data support increased t-PA suppression (without a quantitative decrease in t-PA antigen concentration) secondary to elevated PAI-1 levels immediately following multiple trauma. These changes did not correlate with injury severity. More importantly, the elevated PAI-1 levels did not prevent the breakdown of fibrin by plasmin into D-dimer cross-linked fibrin degradation products.

Antithrombin III

Antithrombin III (AT-III) is a glycoprotein inhibitor of coagulation proteases. Its major effects are inhibition of thrombin, factor Xa, and XIa. Traumatic shock has been found to cause an AT-III deficiency [25].

Heparin (endothelial or exogenous) causes a 1000-fold increase in AT-III activity [17]. Without AT-III, heparin cannot work. Thus an AT-III deficiency could eliminate the effectiveness of subcutaneous heparin injections for DVT prophylaxis. The circulating AT-III concentration may be more important than the heparin dose in conveying antithrombotic protection. Banked whole blood, fresh frozen plasma, and AT-III concentrates can be used to replenish endogenous stores in the acute setting. Tilsner [25] measured AT-III levels on admission in a group of trauma patients. In one-half of the 152 patients without shock symptoms on admission and in two-thirds of the 97 patients with shock symptoms the AT-III levels fell to less than 50% of normal.

Bagge et al. [7] demonstrated reduced AT-III levels in 11 traumatic shock patients admitted to an ICU. This finding was refuted by Enderson et al. [5], who found no significant alterations in AT-III levels during the first three hospital days in a group of severely injured trauma patients. Our data support significant reductions in serum antithrombin III (SAT) immediately following multiple trauma. These changes did not correlate with injury severity.

Protein C Antigen, Functional Protein C, Protein S Antigen

Activated protein C inhibits factors Va and VIIIa, two of the nonproteolytic regulatory proteins (cofactors) of the coagulation cascade. Protein C is activated by the thrombin–thrombomodulin complex on endothelial cells. The activated protein C must then interact with protein S in order to function. Functional protein C is a qualitative test of protein C function, whereas protein C antigen uses a chromogenic method to quantify the protein C concentration in the blood. Inherited forms of protein C and protein S deficiency are both associated with an increased risk of DVT. Acquired protein S deficiency has been seen during pregnancy, after oral contraceptive use, in association with disseminated intravascular coagulation (DIC), and during acute episodes of DVT [10].

Caporale et al. [8] found significantly decreased levels of protein C antigen in 8 of 18 elderly patients undergoing major operations. The patient with the lowest level developed a DVT postoperatively. Our data support a significantly decreased level of both protein C antigen (PrC) and its activity (FPrC) immediately following multiple trauma. The decreases in FPrC were most significant and correlated best with an increase in injury severity (as measured by the ISS). Protein S levels were unchanged following multiple trauma.

D-Dimer

Plasmin acts to cleave cross-linked fibrin plugs, resulting in the production of fibrin degradation products. Plasmin action on the fibrin clot leads to the generation of cross-linked fibrin containing D-dimer [17]. Elevations of D-dimer concentrations indicate active lysis of fibrin. Boneu et al. [26] demonstrated that an elevated D-dimer level, using the ELISA method, was 94% sensitive for DVT.

Bagge et al. [7] demonstrated elevated fibrin degradation products in more than 90% of the blood samples obtained from a group of 11 traumatic shock patients admitted to an ICU. Likewise, Enderson et al. [5] found elevations of D-dimer during the first 3 days of admission in a group of severely injured trauma patients. A significant correlation between D-dimer levels and ISS was not found. Our data support increased D-dimer levels following multiple trauma. Patients with greater injury severity had significantly higher levels of D-dimer. Elevated D-dimer levels probably represent an acute fibrinolytic response to increased thrombin production following significant tissue injury.

Prothrombin Fragment 1.2

As prothrombin is converted to thrombin, the polypeptide prothrombin fragment 1.2 (PF1.2) is released. PF1.2 has a half-life of about 90 minutes. Mean PF1.2 levels are elevated in association with pregnancy, cancer, and old age, and they are depressed in patients receiving warfarin (Coumadin) or heparin [9]. The PF1.2 level has been found in some studies to be higher in antithrombin-deficient patients than in healthy subjects [27]. Our data support elevated PF1.2 levels immediately following multiple trauma. Patients with greater injury severity had significantly higher levels of PF1.2, which definitively demonstrates excessive thrombin production in these patients.

There are several limitations of this study. The effects of variable degrees of resuscitation in the field could not be controlled. Likewise, small differences in the time from injury until presentation in the emergency department may have altered the results. We sought to exclude patients with isolated head injuries from our study under the assumption that gross tissue injury may be responsible for early hypercoagulability. However, the wide variability in patient injuries as well as the shortcomings of the ISS may have limited its correlations. The inclusion of patients with isolated nervous system injury might have resulted in even greater laboratory abnormalities.

The study suggests that a posttraumatic hypercoagulable state occurs within a few hours after injury. Tissue injury may be responsible for the release of tissue factor (thromboplastin), thereby initiating blood coagulation through the conversion of factor VII to enzyme factor VIIa. Tissue factor has been found in fibroblasts and pericytes surrounding blood vessel walls and in the stroma and capsule of many organs and tissues, including the nervous system, lung, heart, skin, and gastrointestinal and genitourinary tracts [28]. Acute brain tissue destruction has been associated with tissue factor-induced DIC [29]. A direct correlation has been found to exist between the ISS and tissue factor generation by monocytes from traumatized patients following an endotoxin stimulus [30]. Additional studies are necessary that correlate tissue factor release and hypercoagulability.

Both D-dimer and PAI-1 are known acute-phase proteins, which may help to explain their significant elevations immediately following a traumatic insult. In addition, many of the other coagulation abnormalities may be secondary to other, as yet uncharacterized endothelial cell-derived inhibitory factors or stress-induced cytokines. The combined effect may be a generalized up-regulation of the inflammatory cascade in an attempt to limit hemorrhage following an acute stress. However, continued

stresses (as seen in an ICU setting) may have the untoward effect of increasing the risk of thrombotic complications. This finding supports the need to provide adequate DVT prophylaxis beginning immediately upon admission to the hospital.

At the present time there are no reliable blood tests to predict which patients may be at increased risk for developing DVT. Enderson et al. [5] showed that the results of standard tests of coagulation (prothrombin time, activated partial thromboplastin time) do not differ significantly between a group of severely injured trauma patients and controls. These measurements of coagulation are not sufficient to identify patients in a hypercoagulable state.

We have identified potential screening tests for the early detection of pathologic hypercoagulability. Identification of a serum marker for trauma patients who are likely to develop DVTs would be beneficial. Positive study markers might encourage clinicians to place these patients on secondary modes of thrombotic prophylaxis that may otherwise not be considered. It could include combined therapies consisting of compression stockings, heparin, dextran, or low-dose warfarin. Those patients who manifest a severely abnormal serum level early in their hospitalization may be considered for prophylactic inferior vena cava filter placement. Likewise, if a significant serum antithrombin III deficiency was documented in a patient with recurrent thromboembolic complications, appropriate transfusions could be given to increase the effectiveness of prophylactic heparin injections. Finally, the serial quantification of these markers may be useful for monitoring the progression of a patient with a consumptive coagulopathy.

Another study is necessary that prospectively correlates these potential screening tests and their alterations over time with the subsequent development of DVT in trauma patients. These serum markers could also prove useful in other high risk populations, such as postoperative patients and patients with prolonged periods of bed rest [7].

Résumé

Dans cette étude, nous avons cherché à mettre en évidence une hypercoagulabilité chez 59 patients ayant un traumatisme grave. Nous avons comparé la concentration d'antigène d'activateur du plasminogène tissulaire (tPA), de l'inhibiteur de l'activation du plasminogène (PAI-I), de l'antithrombine III (SAT), de la protéine C (PrC), de la protéine fonctionnelle (FPrC), de la protéine S (PrS), de la D-dimer et du fragment prothrombine 1-2 à des valeurs de référence. Des signes biologiques d'hypercoagulabilité ont été observés chez 85 ($n = 50$) des patients. Les patients ayant un score de sévérité traumatique (ISS) ≥ 16 ($n = 36$) avaient des taux élevés de D-dimer et des taux diminués de FPrC par rapport aux patients qui avaient un ISS ≤ 15 ($n = 23$). Les taux de protéine fonctionnelle C étaient corrélés négativement avec l'ISS ($r = 0.44$; $p < 0.001$). Un état d'hypercoagulabilité existe immédiatement après un traumatisme sévère. L'hypercoagulabilité semble être proportionnelle au score de sévérité. Les niveaux abaissés de FPrC corrélaient bien aux scores élevés d'ISS.

Resumen

En el presente estudio nos propusimos identificar hipercoagulabilidad en 59 pacientes con trauma severo. Se comparó un perfil de coagulación ampliado, consistente en la concentración de antigeno activador de plasminógeno tisular (tPA), el inhibidor del activador de plasminógeno (PAI-1), antitrombina III, sérica (ISAT), antígeno de proteína C (PrC), proteína C funcional (FPrC), antígeno de proteína S (PrS), D-dimer y fragmento 1.2 de protombina (PF1.2), con valores normales de control. Se halló evidencia de hipercoagulabilidad en 85% ($n = 50$) de los pacientes. Los pacientes con índices de severidad del trauma (ISS, Injury Severity Score) ≥ 16 ($n = 36$) exhibieron niveles significativamente más altos de D-dimer y niveles más bajos de FPrC en comparación con los pacientes con ISS ≤ 15 ($n = 23$). La proteína C funcional demostró una correlación negativa ($r = -0.44$; $p < .001$) con el ISS. Existe un estado de hipercoagulabilidad inmediatamente después del trauma. La mayor severidad de la lesión puede incrementar el estado de hipercoagulabilidad. Niveles disminuidos de FPrC se correlacionan con altos niveles de gravedad de la lesión.

Acknowledgment

This study was supported in part by grants from the Hartford Hospital.

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